General

Guideline Title

The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology.

Bibliographic Source(s)

Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC, Members of LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 2012 Oct;136(10):1266-97. [180 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Summary of Recommendations

Squamous Intraepithelial Lesions, Work Group (WG)2

1. A unified histopathologic nomenclature with a single set of diagnostic terms is recommended for all human papillomavirus (HPV)-associated preinvasive squamous lesions of the lower anogenital tract (LAT).
2. A two-tiered nomenclature is recommended for noninvasive HPV-associated squamous proliferations of the LAT, which may be further qualified with the appropriate –IN (intraepithelial neoplasia) terminology.
   Comment: –IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location, the appropriate complete term should be used. Thus, for an –IN 3 lesion: cervix = CIN 3, vagina = VaIN 3, vulva = VIN 3, anus = AIN 3, perianus = PAIN 3, and penis = PeIN 3.
3. The recommended terminology for HPV-associated squamous lesions of the LAT is low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL), which may be further classified by the applicable –IN subcategorization.

Superficially Invasive Squamous Cell Carcinoma, WG3

1. The term *superficially invasive squamous cell carcinoma* (*SISCCA*) is recommended for minimally invasive squamous cell carcinoma (SCC) of the LAT that has been completely excised and is potentially amenable to conservative surgical therapy.

Comment: Note - Lymph-vascular invasion (LVI) and pattern of invasion are not part of the definition of SISCCA, with the exception of penile carcinoma.

2. For cases of invasive squamous carcinoma *with positive biopsy/resection margins*, the pathology report should state whether:
    - The examined invasive tumor exceeds the dimensions for a SISCCA (defined below) OR
    - The examined invasive tumor component is less than or equal to the dimensions for a SISCCA and conclude that the tumor is "*At least a superficially invasive squamous carcinoma*"
3. In cases of SISCCA, the following parameters should be included in the pathology report:
    - The presence or absence of LVI.
    - The presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma)
4. Cervix: SISCCA of the cervix is defined as an invasive squamous carcinoma that:
    - Is not a grossly visible lesion, AND
    - Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
    - Has a horizontal spread of ≤7 mm in maximal extent, AND
    - Has been completely excised
5. Vagina: No recommendation is offered for early invasive squamous carcinoma of the vagina.
   Comment: Owing to the rarity of primary SCC of the vagina, there are insufficient data to define early invasive squamous carcinoma in the vagina.

6. Anal canal: The *suggested* definition of SISCCA of the anal canal is an invasive squamous carcinoma that:
    - Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
    - Has a horizontal spread of ≤7 mm in maximal extent, AND
    - Has been completely excised
7. Vulva: Vulvar SISCCA is defined as an American Joint Committee on Cancer (AJCC) T1a (International Federation of Gynecology and Obstetrics [FIGO] IA) vulvar cancer. No change in the current definition of T1a vulvar cancer is recommended.
   Comment: Current AJCC definition of T1a vulvar carcinoma:

    - Tumor ≤2 cm in size, confined to the vulva or perineum AND
    - Stromal invasion ≤1 mm
      Note: The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

8. Penis: Penile SISCCA is defined as an AJCC T1a. No change in the current definition of T1a penile cancer is recommended.
   Comment: Current AJCC definition of T1a penile carcinoma:

    - Tumor that invades only the subepithelial connective tissue, AND
    - No LVI AND
    - Is not poorly differentiated (i.e., grade 3–4)
9. Scrotum: No recommendation is offered for early invasive squamous carcinoma of the scrotum.
   Comment: Owing to the rarity of primary SCC of the scrotum, there is insufficient literature to make a recommendation regarding the current AJCC staging of early scrotal cancers.

10. Perianus: The *suggested* definition for SISCCA of the perianus is an invasive squamous carcinoma that:
    - Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
    - Has a horizontal spread of ≤7 mm in maximal extent, AND
    - Has been completely excised

Biomarkers in HPV-Associated Lower Anogenital Squamous Lesions, WG4

1. p16 immunohistochemical is *recommended* when the hematoxylin and eosin (H&E) morphologic differential diagnosis is between precancer (–IN 2 or –IN 3) and a mimic of precancer (e.g., processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting).
   Comment: Strong and diffuse block-positive p16 results support a categorization of precancerous disease.

2. If the pathologist is entertaining an H&E morphologic interpretation of –IN 2 (under the old terminology, which is a biologically equivocal lesion falling between the morphologic changes of HPV infection [low-grade lesion] and precancer), p16 immunohistochemical staining is *recommended* to help clarify the situation. Strong and diffuse block-positive p16 results support a categorization of precancer. Negative or

non–block-positive staining strongly favors an interpretation of low-grade disease or a non–HPV-associated pathology.

3. p16 is *recommended* for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (–IN 2 or –IN 3).
4. WG4 *recommends against* the use of p16 immunohistochemical staining as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, –IN 1, and –IN 3.
    a. Special Circumstance: p16 immunohistochemistry (IHC) is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as ≤–IN 1 that are at high risk for missed high grade disease, which is defined as a prior cytologic interpretation of HSIL, high grade atypical squamous cells (ASC-H), atypical squamous cells of undetermined significance (ASC-US)/HPV-16+, or atypical glandular cells not otherwise specified (AGC [NOS]).

    Comment: Any identified p16-positive area must meet H&E morphologic criteria for a high-grade lesion to be reinterpreted as such.

Clinical Algorithm(s)

Algorithms for biomarkers in human papillomavirus (HPV)-associated lower anogenital squamous lesions are available in a separate document (see the "Availability of Companion Documents" field).

Scope

Disease/Condition(s)

Human papillomavirus (HPV)–associated squamous lesions of the lower anogenital tract

Guideline Category

Diagnosis

Evaluation

Management

Clinical Specialty

Colon and Rectal Surgery

Dermatology

Family Practice

Gastroenterology

Infectious Diseases

Internal Medicine

Obstetrics and Gynecology

Oncology

Pathology

Preventive Medicine

Surgery

Urology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

- To create a histopathologic nomenclature system that reflects current knowledge of human papillomavirus (HPV) biology, optimally uses available biomarkers, and facilitates clear communication across different medical specialties
- The project had several specific objectives carried out by 5 work groups:
  - To develop a historical perspective of the origins of terminologies in the lower anogenital tract, with an emphasis on how nomenclature has influenced management
  - To address whether the biology of HPV-associated disease in all of these sites allowed for unification of terminology
  - To propose terminology for intraepithelial lesions and early invasive carcinoma
  - To perform a review to determine whether currently available biomarkers support any proposed terminology recommendations or improve diagnostic reliability and reproducibility of histopathologic interpretation
  - To facilitate and monitor dissemination and implementation of terminology changes into clinical practice with the goal of optimizing educational, quality assurance, regulatory, and clinical processes

Target Population

Patients with known or suspected human papillomavirus (HPV)–associated squamous lesions of the lower anogenital tract

Interventions and Practices Considered

Unified histopathologic nomenclature with a single set of diagnostic terms for:

- *Squamous intraepithelial lesions* (e.g., low-grade [LSIL] and high-grade squamous intraepithelial lesion [HSIL])
- *Superficially invasive squamous cell carcinoma (SISCCA)*, including definitions for SISCCA of the cervix, vagina, anal canal, vulva, penis, scrotum, perianus
- *Biomarkers in HPV-associated lower anogenital squamous lesions* (e.g., p16, p16 immunohistochemistry [IHC])

Major Outcomes Considered

- Terminologies used for human papillomavirus (HPV)-related lower anogenital tract mucocutaneous intraepithelial and primary invasive neoplasia
- Clinical management strategies for HPV-related lower anogenital tract mucocutaneous intraepithelial and primary invasive neoplasia
- Molecular markers for lower anogenital tract mucocutaneous intraepithelial and primary invasive neoplasia

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Review

A computerized search was conducted for 4 of the 5 Work Groups (WGs) using the following electronic databases: OVID MEDLINE, PubMed, Wiley Cochrane Library, and OCLC WorldCat, for English-language articles only. All study designs and publication types were included. Reference lists from identified articles were examined for articles not identified in the searches. The scope, key questions, search terms as defined by the SC, and the literature review results are displayed in the supplemental methodology material (see Appendix, Supplemental Digital Content; see the "Availability of Companion Documents" field). Screening and data extraction were completed using DistillerSR (Evidence Partners, Ottawa, Canada) for WG2, 3, and 4.

Each identified article underwent an inclusion-exclusion process, dual-independent reviews conducted by co-chairs and WG members. On the basis of each WG's inclusion-exclusion criteria, articles were kept for full data extraction, as "'indirect background material,'" or excluded from further review. Articles with 2 differing votes were considered in "'conflict.'" Conflicts were adjudicated by both reviewers for WG2 and WG3 and by co-chair referees when conflicts could not be resolved. Co-chairs alone adjudicated WG4 conflicts. Conflicts included the "uncertain" reviews at the title/abstract level and the "indirect background material" reviews at the full text level.

Number of Source Documents

For Work Group 2 (Squamous Intraepithelial Lesions), 1909 studies met the search term requirements and 186 studies were included for data extraction. For Work Group 3 (Superficially Invasive Squamous Cell Carcinomas) 1863 studies met the search term requirements and 194 studies were included for data extraction. For Work Group 4 (Biomarkers in human papillomavirus [HPV]-associated Lower Anogenital Squamous Lesions), 2291 studies met the search term requirements; 72 studies were included for data extraction, and 18 studies identified for grading (see the Supplemental Digital Content for more information; see the Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Quality of Evidence

An independent assessment of the quality of the data was conducted for Work Group (WG) 4 (Biomarkers in human papillomavirus [HPV]-associated Lower Anogenital Squamous Lesions) since the recommendations for WG4 were driven most by the data extractions. WG2 and WG3 members completed and reviewed their data extraction; their respective literature reviews and proposed recommendations are based upon expert opinion with the appropriate references provided.

Methods Used to Formulate the Recommendations

Expert Consensus (Consensus Development Conference)

Description of Methods Used to Formulate the Recommendations

A consensus process was convened to recommend terminology unified across lower anogenital sites. The goal was to create a histopathologic nomenclature system that reflects current knowledge of HPV biology, optimally uses available biomarkers, and facilitates clear communication across different medical specialties. The Lower Anogenital Squamous Terminology (LAST) Project was designed to comprehensively evaluate the terminology of human papillomavirus (HPV)-associated squamous lesions of the lower anogenital tract (LAT), including the cervix, the vagina, the vulva, the perianus, the anus, the penis, and the scrotum. The LAST Project included 5 working groups; 3 work groups performed comprehensive literature reviews and developed draft recommendations. Another work group provided the historical background and the fifth will continue to foster implementation of the LAST recommendations.

After data extractions, Work Group members crafted draft summations and recommendations. The drafts were posted on the American Society for Colposcopy and Cervical Pathology (ASCCP) Web site for open comment for 26 days from mid-January to mid-February 2012. After review of the open comments, draft recommendations were revised, if needed, before the consensus conference held immediately preceding the March of 2012 ASCCP Biennial Meeting in San Francisco, CA.

Recommendations for terminology of squamous intraepithelial lesions (WG2) and superficially invasive squamous carcinomas (WG3) were based on the expert opinion of WG members and advisors after their comprehensive review of the literature. The recommendations from WG4, on use of biomarkers, were chiefly driven by the specific data from the comprehensive literature review. Based on the reviewer's overall assessment of the quality of the evidence for test characteristics and observer variability, Work Group 4's recommendations were framed using "recommend" if the recommendations are unlikely to change based on further evidence, and "suggest" if the recommendations are most likely correct but could be better supported by additional data.

At the consensus conference, WG members and advisors, along with representatives from 35 participating organizations (see Table 5, Supplemental Digital Content; see the "Availability of Companion Documents" field) and observers, deliberated on, revised, and voted on the final draft recommendations; observers did not vote. At least a two-thirds majority (67%) was required for passage of each recommendation. The LAST Project writing committee was tasked with adding to the documentation the appropriate supporting detail and explanatory material for the recommendations.

See the Supplemental Digital Content (see the "Availability of Companion Documents" field) for more information on panel composition and methods used to produce recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The College of American Pathologists (CAP) Independent Review Panel and the Transformation Program Office Steering Committee provided final review and approval of the manuscript. The American Society for Colposcopy and Cervical Pathology (ASCCP) Executive Board also reviewed prior to submission of the manuscript.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Standardization of lower anogenital squamous terminology for human papillomavirus (HPV)-associated lesions

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

College of American Pathologists (CAP)-American Society for Clinical Pathology (ASCCP) Consensus Statement

The College of American Pathologists developed the Pathology and Laboratory Quality Center as a forum to create and maintain evidence-based practice guidelines and consensus statements. Practice guidelines and consensus statements reflect the best available evidence and expert consensus supported in practice. They are intended to assist physicians and patients in clinical decision-making and to identify questions and settings for further research. With the rapid flow of scientific information, new evidence may emerge between the time a practice guideline or consensus statement is developed and when it is published or read. Guidelines and statements are not continually updated and may not reflect the most recent evidence. Guidelines and statements address only the topics specifically identified therein and are not applicable to other interventions, diseases, or stages of diseases. Furthermore, guidelines and statements cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge, to determine the best course of treatment for the patient. Accordingly, adherence to any practice guideline or consensus statement is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances and preferences. CAP and ASCCP assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this statement or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

Implications and Implementation of Standardized Terminology - Work Group 5

The overall scope and purpose of Work Group 5 was to address the potential implications of the Lower Anogenital Squamous Terminology (LAST) Project recommendations and to develop and initiate action plans for implementation of the recommendations.

Effective communication is absolutely necessary for widespread acceptance and adoption to occur. As with the Bethesda System terminology for gynecologic cytology, widespread communication of the benefits of changing and unifying terminology was necessary before adoption occurred. Likewise, the Work Group identified communities of interest for the LAST Project recommendations to include patients and patient advocacy groups; pathologists; treating physicians including gynecologists, primary care providers, dermatologists, gynecologic oncologists, infectious disease

specialists, colorectal surgeons, urologists, and others; and nurse practitioners and other allied health professionals; government, regulatory, and nomenclature agencies including the Centers for Medicare and Medicaid Services, the Joint Commission, American Joint Committee on Cancer, the International Federation of Gynecology and Obstetrics, the Society of Gynecologic Oncologists, World Health Organization, and others; public health, research, and surveillance organizations such as the Centers for Disease Control and Prevention, Surveillance Epidemiology and End Results, and tumor registries; educational, training, and testing organizations including specialty societies, training facilities, examination boards, publications and scientific literature; and payers and Current Procedural Terminology and International Classification of Disease coding organizations.

To communicate to these communities of interest, the Work Group recommended sustained organizational support to aid in the dissemination of the LAST recommendations. Specific actions include support for guideline publication; promote editorial commentaries for journals in related fields; present summary recommendations at scientific meetings; produce educational materials for professionals and patients; and develop a Web site that will include reference images, sample reports, and a self-test.

One of the major concerns raised by the clinical community regards management of cervical lesions in young women. The American Society for Colposcopy and Cervical Pathology (ASCCP) will address specific issues related to its clinical management guidelines in the near future. A potential reconciliation of the LAST terminology and the 3-tiered cervical intraepithelial neoplasia (CIN) system with current clinical management is represented in Figure 20 of the original guideline document.

Many of these recommendations have already been initiated and will continue to be developed further. It is also imperative to have liaison with professional organizations to assess current practice regarding use of LAST terminology for squamous human papillomavirus (HPV)-associated lesions and associated biomarker usage and to monitor adoption of the LAST recommendations.

Implementation Tools

Clinical Algorithm

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC, Members of LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 2012 Oct;136(10):1266-97. [180 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Oct

Guideline Developer(s)

American Society for Colposcopy and Cervical Pathology - Medical Specialty Society

College of American Pathologists - Medical Specialty Society

Source(s) of Funding

The American Society for Colposcopy and Cervical Pathology (ASCCP) and College of American Pathologists (CAP) provided the funding for this project; no industry funds were used in the development of the consensus statements and recommendations.

Guideline Committee

Lower Anogenital Squamous Terminology (LAST) Steering Committee

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Financial Disclosures/Conflicts of Interest

Management of Conflicts of Interest

All expert panel members complied with the College of American Pathologists (CAP) conflicts of interest policy (in effect, October 2010), which required disclosure of financial or other interests that may have an actual, potential, or apparent conflict (see Appendix, Supplemental Digital Content; see the "Availability of Companion Documents" field). See the original guideline document for declarations of conflicts of interest by the Lower Anogenital Squamous Terminology (LAST) Steering Committee members, Work Group members, and/or Conference Moderators.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Archives of Pathology & Laboratory Medicine Web site .

Availability of Companion Documents

The following are available:

- CAP/ASCCP lower anogenital squamous terminology for HPV-associated lesions. Summary of consensus recommendations. 2012. 2 p. Electronic copies: Available in Portable Document Format (PDF) from the College of American Pathologists (CAP) Web site .
- Biomarkers in HPV-associated lower anogenital squamous lesions from the CAP-ASCCP Lower Anogenital Squamous Terminology Project. Webinar. Available from the CAP Web site .
- LAST biomarkers for HPV-associated lesions algorithm chart. 2012 11 p. Electronic copies: Available in PDF from the CAP Web site .
- Lower Anogenital Squamous Terminology standardization of HPV-associated neoplasia. PowerPoint presentation. 2012. 130 p. Electronic copies: Available in PDF from the CAP Web site .
- Frequently asked questions (FAQs). 2012. 7 p. Electronic copies: Available from the CAP Web site .

Supplemental digital content is available from the Lippincott Williams & Wilkins Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 17, 2013. The information was verified by the guideline developer on June 12, 2013.

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